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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/591,737	06/12/2000	David F. Curiel	D6167CIP	3628

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 10/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/591,737	Applicant(s) CURIEL ET AL
	Examiner Janice Li	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b)

Status

1)☒ Responsive to communication(s) filed on *16 July 2002*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-17,19-21,23-31 and 33-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-17,19-21,23-31 and 33-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f)

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). ☒ Other: detailed action

DETAILED ACTION

The Declaration under 37 C.F. R. § 1.132 and amendment filed on July, 2002 have been entered as Papers #9 & 10. Claims 1, 11, 14, 17, 21, 40, 43, 53, and 55 have been amended. Claims 1, 3-17, 19-21, 23-31, and 33-56 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

ENABLEMENT REQUIREMENT

Claims 11-17, 19-21, 23, 24, 27-30, 40-45, and 53-56 stand rejected for the reasons of record and following.

In paper #10, applicants argue repeatedly that the claims are drawn to methods of gene transfer, not treatment of disease, and not the efficacy of DNA vaccines.

The arguments have been carefully considered but found not persuasive. This is because given the broadest reasonable interpretation, the claim recitation, "a method for enhancing dendritic cell-based vaccination...wherein said gene delivery increases

consisting of cancer, an infectious disease, allotransplant rejection, xenotransplant rejection and an autoimmune disease", clearly and/or implicitly claiming the treatment aspect of a vaccine and the efficacy of DNA vaccines.

In the Declaration under 37 C.F. R. § 1.132, applicants submitted experimental data to indicate that the claimed gene delivery system could target the Adv vector to ovarian cancer cells in vitro, increasing selectivity of the vector and maturation of dendritic cells in human skin explants, thus, demonstrated that the delivery system could selectively manipulating CD40+ immune cells, and increasing gene delivery and causing maturation of said immune cells.

However, as indicated in Papers #4 and 7, the teachings in the gene therapy art suggest that the efficacy of a DNA vaccine is determined by numerous factors. For example, *Bodey et al* (Anticancer Res 2000;20:2665-76) teach, "THE CANCER VACCINE APPROACH TO THERAPY IS BASED ON THE NOTION THAT THE IMMUNE SYSTEM COULD POSSIBLY MOUNT A REJECTION STRENGTH RESPONSE AGAINST THE NEOPLASTICALLY TRANSFORMED CELL CONGLOMERATE. HOWEVER, DUE TO THE LOW IMMUNOGENICITY OF TUMOR ASSOCIATED ANTIGENS, DOWNREGULATION OF MHC MOLECULES, THE LACK OF ADEQUATE COSTIMULATORY MOLECULE EXPRESSION, SECRETION OF IMMUNE INHIBITORY CYTOKINES, ETC., SUCH EXPECTATION ARE RARELY FULFILLED..." (page 2665, column one). *Radoja et al* (Mol Med 2000;6:465-79) teach, "THE NOTION THAT A DEFICIT IN IMMUNE CELL FUNCTIONS PERMITS TUMOR GROWTH HAS RECEIVED EXPERIMENTAL SUPPORT WITH THE DISCOVERY OF SEVERAL DIFFERENT BIOCHEMICAL DEFECTS IN T LYMPHOCYTES THAT INFILTRATE CANCERS" (abstract). "ACCUMULATION OF CIRCULATING ANTITUMOR IMMUNOGLOBULIN G IN CANCER PATIENTS SHOW THAT THE PRIMING PHASE OF

TUMOR GROWTH... IN BOTH HUMAN CANCER PATIENTS AND RODENTS BEARING TUMORS OF DIFFERENT HISTOLOGIC ORIGIN, SYSTEMIC IMMUNITY IS NOT PROFOUNDLY SUPPRESSED..." "HOWEVER, INHIBITION OF A SPECIFIC ANTITUMOR IMMUNE RESPONSE HAS NOT BEEN OBSERVED FREQUENTLY. A VARIETY OF MECHANISM HAVE BEEN PROPOSED TO ACCOUNT FOR DEFECTIVE ANTITUMOR IMMUNE RESPONSE, INCLUDING: SECRETION OF SUPPRESSIVE FACTORS IN THE TUMOR MICROENVIRONMENT, THE LACK OF EXPRESSION OF COSTIMULATORY SIGNALS ON TUMOR CELLS, INDUCTION OF REGULATORY T CELLS HAVING A SUPPRESSIVE PHENOTYPE, LOSS OF ANTIGEN PRESENTATION FUNCTION IN THE TUMOR, LOSS OF EXPRESSION OF HLA CLASS I ANTIGEN PRESENTING MOLECULES IN TUMORS, TUMOR-INDUCED T-CELL SIGNALING DEFECTS, LOSS OF TUMOR ANTIGEN EXPRESSION, IMMUNOLOGICAL IGNORANCE AND, SINCE MANY TUMOR ANTIGENS ARE EITHER UNMODIFIED SELF OR EPITOPES CLOSELY RELATED TO SELF, THE REDUCTION OF THE REPERTOIRE OF POTENTIAL HIGH AFFINITY ANTITUMOR T-CELL CLONES DURING T-CELL MATURATION IN THE THYMUS" (Introduction). Apparently, enhanced transduction of dendritic cells may enhance the gene targeting and dendritic cell maturation, however, this is only the first step in a long way to the enhanced efficacy of a DNA vaccination, many other factors, as taught by *Boedy et al* and *Radoja et al*, would affect the overall efficacy of cancer DNA vaccine, the fate of an allogenic and/or xenogenic graft, and the outcome of an autoimmune disease.

Considering numerous factors that may contribute to the efficacy of the DNA vaccines for the recited diseases, particularly, the fact that the priming phase of the immune response in cancer patients was not significantly altered, it is highly unpredictable whether the overall vaccination efficacy would be enhanced in those patients by providing a bi-specific gene delivery system as instantly claimed.

Accordingly, in view of the quantity of experimentation necessary to determine the enhanced vaccination efficacy for any given disease recited in the claims, the lack of direction or guidance provided by the specification with regard to the breadth of the claims directed to enhanced DNA vaccination efficacy in patients with tumor, allograft, xenograft rejection, and autoimmune diseases, it would have required undue experimentation for one skilled in the art to practice the claimed invention as they are broadly claimed.

For the reasons of record and those set forth above, the instant specification fails to meet the enablement requirement.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-10, 25, 26, 31, 33-37, and 46-50 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over

Applicants argue in Paper #10 that claims 31 and 46 are drawn to genetically modified adenovirus having a fiber protein comprising CD40 ligand, in one embodiment, the fiber shaft of the fiber protein is further replaced by bacteriophage T4 fibritin protein as exemplified in example 7, whereas claims of '742 patent did not teach or suggest a genetically modified adenovirus having a fiber protein comprising CD40 lighand as claimed herein. Accordingly, applicants request that the rejection of claims 31, 33-27 and 46-50 be withdrawn.

The arguments have been carefully considered but found not persuasive.

First, even though claim 1 of the cited patent does not recite the term, "recombinant" or "genetically modified", "AN ADENOVIRAUS ENCODING A GENE OF INTEREST" is a genetically modified, recombinant adenovirus. This assertion is also supported by the teachings throughout the '742 patent. For example, the specification of the cited patent teaches using tropism-modified adenoviral vectors for targeted gene delivery (column 2, lines 10-14).

Secondly, the instant recitation, "a genetically modified adenovirus having a fiber protein comprising CD40 ligand" still embraces claim 1 of the cited patent. This is because instant claims 31 and 46 do not require a modification of T4 fibritin protein replacement, and the specification of '742 patent defines the adenovirus provided by the invention, as "WHEREIN THE ADENOVIRAL GENE ENCODING A FIBER KNOB PROTEIN HAS BEEN REPLACED WITH A GENE ENCODING ... THE NATURAL LIGAND OF CD40, THE TRIMERIC CD40 LIGAND" (paragraph bridging columns 3 & 4). Because the natural ligand of CD40 comprises the

globular domain as claim 46 recites, the subject matter of claims 31 and 46 of the pending application is fully disclosed in the cited patent.

Accordingly, the claimed system in the cited patent and the present application are obvious variants. Therefore, the inventions as claimed are co-extensive.

Claims 1, 3-10, 25, 26, 31, 33-39, and 46-52 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,284,742 in view of *Krul et al* (Cancer Immunol Immmunother 1996;43:44-48) for reasons of record advanced in Paper #7.

Applicants do not present any argument to this rejection. Thus, the rejection stands.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
September 30, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER